

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 82300416.3

(22) Date of filing: 27.01.82

(51) Int. Cl.<sup>3</sup>: **A 61 K 37/02**  
**C 08 G 63/08**  
**//C07C103/52, A61K31/765,**  
**A61K9/22**

(30) Priority: 16.02.81 GB 8104734

(43) Date of publication of application:  
25.08.82 Bulletin 82/34

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: **IMPERIAL CHEMICAL INDUSTRIES PLC**  
**Imperial Chemical House Millbank**  
**London SW1P 3JF(GB)**

(72) Inventor: **Hutchinson, Francis Gowland**  
**29 Woodland Drive**  
**Lymm Cheshire WA13 0BL(GB)**

(74) Representative: **Atkinson, John David et al,**  
**Imperial Chemical Industries PLC Legal Department :**  
**Patents Thames House North Millbank**  
**London SW1P 4QG(GB)**

(54) **Continuous release pharmaceutical compositions.**

(57) Pharmaceutical compositions, comprising a polylactide and a pharmacologically active, acid stable polypeptide, which when placed in an aqueous physiological environment release the polypeptide at an approximately constant rate in an essentially monophasic manner, with a minimal, or no induction period prior to the release; polylactides suitable for use in said compositions; and a method for the manufacture of such polylactides.

**EP 0 058 481 A1**

TITLE: CONTINUOUS RELEASE PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions of pharmacologically-active acid-stable polypeptides, which provide continuous release of the polypeptide over an extended period when the composition is placed in an aqueous, physiological-type environment.

It has long been appreciated that the continuous release of certain drugs over an extended period following a single administration could have significant practical advantages in clinical practice, and compositions have already been developed to provide extended release of a number of clinically useful drugs, after oral dosing (see, for example, Remington's Pharmaceutical Sciences, published by Mack Publishing Company, Easton, Pennsylvania, U.S.A., 15th Edition, 1975, pages 1618-1631), after parenteral administration (*ibidem*, pages 1631-1643), and after topical administration (see, for example, United Kingdom Patent Number 1,351,409). A suitable method of parenteral administration is the sub-dermal injection or implantation of a solid body, for example a pellet or a film, containing the drug, and a variety of such implantable devices has been described. In particular, it is known that, for many drugs, suitable implantable devices for providing extended drug release may be obtained by encapsulating the drug in a biodegradable polymer, or by dispersing the drug in a matrix of such a polymer, so that the drug is released as the degradation of the polymer matrix proceeds.

- 2 -

Suitable biodegradable polymers for use in sustained release formulations are well known, and include polyesters, which gradually become degraded by hydrolysis when placed in an aqueous, physiological-type environment. Particular polyesters which have been used are those derived from hydroxycarboxylic acids, and much prior art has been directed to polymers derived from  $\alpha$ -hydroxycarboxylic acids, especially lactic acid in both its racemic and optically active forms, and glycolic acid, and copolymers thereof - see, for example, United States Patents Numbers 3,773,919 and 3,887,699; Jackanicz et al., Contraception, 1973, 8, 227-234; Anderson et al., ibidem, 1976, 11, 375-384; Wise et al., Life Sciences, 1976, 19, 867-874; Woodland et al., Journal of Medicinal Chemistry, 1973, 16, 897-901; Volles et al., Bulletin of the Parenteral Drug Association, 1976, 30, 306-312; Wise et al., Journal of Pharmacy and Pharmacology, 1978, 30, 686-689 and 1979, 31, 201-204.

In this specification, the term "polylactide" is used in a generic sense to include polymers of lactic acid alone, copolymers of lactic acid and glycolic acid, mixtures of such polymers, mixtures of such copolymers, and mixtures of such polymers and copolymers, the lactic acid being either in racemic or in optically active form. Also, the term "acid-stable" is to be understood as meaning that the polypeptide is not significantly hydrolysed under the conditions encountered within the claimed formulations during the period of use envisaged, that is, at pH 2 at mammalian body temperature, say up to 40°C., for up to six months.

## United Kingdom Patent Specification

Number 1,325,209 (equivalent to United States Patent Specification Number 3,773,919) and United States Patent Specification Number 3,887,669 is the only  
5 prior art known to us which makes any reference to extended or sustained release of polypeptides, the latter mentioning insulin only, but it contains no specific example of any such formulation, and the reference to polypeptides is apparently entirely  
10 speculative, appearing, as it does, only in an extensive listing of very many different classes of drugs which can allegedly be incorporated into formulations of the kind described therein. In fact, essentially all of the other drug types referred to in  
15 that specification, apart from polypeptides, are relatively hydrophobic in character and of relatively low molecular weight, and the disclosure of that specification displays no recognition of the difficulties which we have encountered when seeking to obtain  
20 satisfactory sustained release formulations of polypeptides, many of which are relatively hydrophilic, and of relatively high molecular weight.

It is to be appreciated that "sustained" or "extended" release of a drug may be either continuous  
25 or discontinuous. We have now discovered, in fact, that in many cases when the teaching of the prior art, and in particular the teaching of United Kingdom Specification No. 1,325,209, is applied to the manufacture of a formulation of an acid-stable  
30 polypeptide, the release of the polypeptide from the formulation, although occurring over an extended period of time, may also be discontinuous. For example, the release of a polypeptide from a polylactide polymer as described in the said Specification is often preceded

- 4 -

by a significant induction period, during which no polypeptide is released, or is biphasic, and comprises an initial period during which some polypeptide is released, a second period during which little or no polypeptide is released, and a third period during which most of the remainder of the polypeptide is released. By contrast, it is an object of the present invention to provide compositions of acid-stable polypeptides from which, apart possibly from a relatively short initial induction period, the polypeptide is released continuously, with no periods during which little or no polypeptide is released. The words "continuous release" are used in this specification solely to describe a release profile which is essentially monophasic, although it may have a point of inflection, but certainly has no "plateau" phase.

Thus, according to the present invention, there is provided a pharmaceutical composition comprising a polylactide, as hereinbefore defined, and an acid-stable polypeptide, which, when placed in an aqueous physiological-type environment, releases polypeptide into said aqueous physiological-type environment in a continuous manner, as hereinbefore defined, until essentially all of the polypeptide has been released.

This invention is applicable to acid-stable polypeptides quite generally, without any limitation as to structure or molecular weight, but is most useful for polypeptides which are relatively hydrophilic, and the following list, which is not intended to be exhaustive, is indicative of polypeptides which may be employed in the formulation of this invention:-

- 5 -

oxytocin, vasopressin, adrenocorticotrophic hormone (ACTH), epidermal growth factor (EGF), prolactin, luteinizing hormone releasing hormone (LH-RH), insulin, somatostatin, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidin, gramicidines, and synthetic analogues and modifications and pharmacologically-active fragments thereof.

We have found, however, that polypeptides which are not stable under acid conditions, are unsuitable for use in the compositions of this invention, as they become degraded in the acid environment produced in the polymer matrix when the polyactide starts to degrade by hydrolysis, thus producing carboxylic acid end groups.

By "an aqueous physiological-type environment" we mean the body, particularly the musculature or the circulatory system, of a warm-blooded animal, although in laboratory investigations such an environment may be mimicked by aqueous liquids, optionally buffered to a physiological pH, at a temperature of between 35 and 40°C.

The continuous release composition of the invention may be placed in the body of an animal which it is desired to treat with a polypeptide by, for example, intramuscular or subcutaneous injection, or by sub-dermal surgical implantation, in conventional clinical or veterinary manner.

- 6 -

We have discovered that a pharmaceutical composition according to the invention may be designed to provide continuous release of the polypeptide by the appropriate choice or control of various parameters, for example by varying the polylactide composition, particularly the proportion of lactic acid to glycolic acid in copolymers; by controlling the molecular weight of the polylactide, both the weight-average molecular weight, and the molecular weight range or polydispersity, measured by the ratio of the weight-average molecular weight, ( $M_w$ ), to the number-average molecular weight ( $M_n$ ), i.e.  $\frac{M_w}{M_n}$ ; by choice of the proportion of polypeptide to polylactide; or by choice of the geometry of a solid formulation for implantation, or of the particle size in a formulation for injection. The release characteristics of such compositions are also controlled to some extent by the nature of the polypeptide itself. In particular, there is less freedom of choice in defining the parameters mentioned above when designing a composition of the invention for a polypeptide of high molecular weight, (say, greater than 6000), than there is when designing a composition for a polypeptide of lower molecular weight, (say, less than 6000).

We have further discovered that the release of a polypeptide from a composition comprising a polylactide and a polypeptide proceeds by two distinct and independent mechanisms, namely first a diffusion-dependent release of polypeptide out of the polylactide-polypeptide matrix comprising leaching from the surface, and, for low molecular weight polypeptides, some

- 7 -

partition-dependent diffusion of polypeptide per se; and subsequently, as the polylactide becomes degraded, diffusion of aqueous polypeptide solution out of the composition through aqueous channels.

5                   In general, the compatibility of polypeptides in polylactide polymers is limited, except in the case of low molecular weight (up to, say, 6000 molecular weight) polypeptides which are capable of having some specific interaction with the polylactide, for example  
10 a low molecular weight polypeptide which is basic, and which therefore interacts with the terminal carboxylic acid groups in the polylactide. Because of this limited compatibility of polypeptide in polylactide, a polypeptide/polylactide formulation, when placed in  
15 an aqueous environment, releases very little polypeptide by diffusion through the polymer matrix. While this is broadly true for all combinations of polypeptide and polylactide, matrix diffusion is at a minimum for high molecular weight polypeptides in high molecular  
20 weight polylactides. Even when some matrix diffusion resulting in polypeptide release occurs initially on placing the composition in an aqueous environment, by release from or very near the surface, this soon ceases because the diffusion of polypeptide into polylactide  
25 is insufficient to result in continuous transport of polypeptide from inside the composition to its surface.

When a polypeptide/polylactide composition is placed in an aqueous environment, water diffuses into the matrix, and is partitioned between polypeptide  
30 and polylactide to form domains of aqueous polypeptide solution. This aqueous polypeptide, obtained when absorbed water is partitioned between polypeptide and



polylactide, is incompatible with, and insoluble in, polylactides, particularly those of high molecular weight, so that absorption of water by the composition still further reduces initially any likelihood of matrix diffusion of polypeptide out of the composition. If the aqueous domains of polypeptide so formed are discrete and isolated, then the compositions are incapable of releasing polypeptide. However, the possibility of the aqueous polypeptide domains having some continuity increases with increasing concentration of polypeptide in the composition, and with increasing absorption of water, and when the continuity of aqueous polypeptide domains reaches a sufficient level to communicate with the exterior surface of the composition, polypeptide starts to be released from the formulation by diffusion, not through the polylactide matrix, but through aqueous polypeptide channels. Even when some aqueous polypeptide domains near the surface have extended so as to reach the exterior of the composition, that aqueous polypeptide which exists in still isolated domains is not released, and is only released when a secondary hydrophilic path for diffusion becomes available. For high molecular weight polylactides, this secondary hydrophilic diffusion path arises when the polylactide has undergone sufficient degradation for the rate of absorption of water to increase significantly. When this occurs, aqueous pores or channels are generated in the polylactide matrix, which allow a continuous and significant release of polypeptide, as aqueous solution, from previously discrete and isolated domains.

- 9 -

As indicated above, we have discovered that, when sustained release compositions of the prior art, and particularly those described in United Kingdom Patent Specification Number 1,325,209, are used for the release  
5 of polypeptides, the initial matrix diffusion phase of polypeptide release, and the secondary release of polypeptide consequent upon degradation of the polylactide, are separated in time with the result that the release of polypeptide is not continuous, but  
10 is biphasic and discontinuous, comprising a small first release of polypeptide, a dead phase during which essentially no polypeptide is released, and a subsequent second release phase, during which substantially all of the remaining polypeptide is released. We have  
15 now discovered that, by appropriate choice of the parameters of the composition, the matrix diffusion phase of release, and the subsequent degradation induced phase of release, can be made to overlap in time.

20 Thus, according to a further feature of the invention there is provided a pharmaceutical composition comprising a polylactide, as hereinbefore defined, and an acid-stable polypeptide, and exhibiting two successive phases of release of polypeptide when placed in an  
25 aqueous physiological-type environment, the first phase being release by matrix diffusion and the second phase being release consequent upon degradation of the polylactide, characterised in that the diffusion phase and the degradation-induced phase overlap in time.

30 The two phases can be made to overlap by either extending the initial diffusion phase, or making the degradation-induced phase commence earlier, or both.

- 10 -

The initial matrix release phase is difficult to extend, but is sensitive to the concentration of the polypeptide in the matrix, and to a limited extent, to the nature of the polypeptide, especially its hydrophilicity,

The degradation-induced release phase can be made to start sooner by appropriate choice of polylactide composition (more glycolide-rich polymer molecules, which degrade more quickly than lactide-rich molecules),  $M_w$  (molecules of low molecular weight degrade more quickly to a level at which aqueous channels appear in the matrix), and polypeptide concentration (a higher polypeptide concentration allows more rapid absorption of water, and consequently more rapid generation of continuous aqueous channels which facilitate polypeptide release).

However, as well as requiring the degradation-induced release phase to start earlier, it is also necessary to control the rate of polypeptide release during this phase, and to ensure that the total duration of this phase is sufficient for its intended clinical or veterinary purpose. One method of extending the duration of the degradation-induced release phase, is to use polylactides which contain lactide-rich molecules, which degrade more slowly than glycolide-rich molecules, or alternatively, polylactides containing molecules of high molecular weight, which take longer to degrade to a level at which aqueous channels are formed, can be used.

- 11 -

It is apparent, therefore, that since glycolide-rich polymer molecules, and/or molecules of low molecular weight, are preferred if the degradation phase is to start quickly, and lactide-rich molecules, and/or molecules of high molecular weight are preferred if the degradation-induced release phase is to last for a sufficient period of time, preferred polylactides are those with a high degree of heterogeneity, in respect of glycolide-rich and lactide-rich molecules, or of high polydispersity.

Alternatively, the same characteristics can be obtained by blending two or more different polylactides, which differ in lactide/glycolide content, and/or in  $M_w$ . In addition, the blending of a minor proportion of polylactide of high  $M_w$  with a polylactide of low  $M_w$ , confers desirable physical properties upon compositions according to this invention produced therefrom, making them easier to fabricate and process.

We have further discovered that the profile of polypeptide release from both prior art polylactides and novel polylactides is almost exactly paralleled by the profile of water absorption. That is to say, when polypeptide release is discontinuous, water absorption is also discontinuous in essentially the same manner, and conversely, when polypeptide release is continuous, so is water absorption. Furthermore, variation of the parameters referred to above for controlling the polypeptide release characteristics of the composition have been found to affect water absorption by the composition in an exactly parallel manner.

- 12 -

Thus, according to a further feature of the invention there is provided a pharmaceutical composition, comprising a polylactide as hereinbefore defined and an acid-stable polypeptide, which when placed in an aqueous physiological-type environment absorbs water in a continuous manner, as hereinbefore defined, until the polylactide has been degraded and essentially all of the polypeptide has been released into said aqueous physiological-type environment.

The effect of the various parameters, referred to above, on the polypeptide release and/or water absorption characteristics of compositions of the invention is illustrated by the following experiments:-

A. Molecular weight of the polylactide component.

A.1. Low molecular weight polypeptide.

A.1.1. Formulations were manufactured comprising 20% w/w of the gastric peptide fragment tetragastrin hydrochloride, Trp-Met-Asp-Phe-NH<sub>2</sub>.HCl, molecular weight = 633, in a polylactide comprising equimolar proportions of D,L-lactide and glycolide units, in the form of a film 0.2mm. thick. The films were placed individually in water at 37°C., which was changed daily, and the ultra-violet absorption at 277nm. was measured to assay the tetragastrin released by the formulation that day.

With a prior art type of polylactide of  $M_w$  approximately 240,000 (intrinsic viscosity = 1.36), there was an initial release of tetragastrin, then a "dead period" from about day 5 to day 21 during

- 13 -

which little was released, followed by the main release from day 24 onward.

5 With a novel polylactide of  $M_w$  approximately 15,000 (intrinsic viscosity = 0.25), the release pattern was similar, but the dead period lasted only from day 4 or 5 to day 8 or 9.

10 With a novel polylactide of low  $M_w$  (inherent viscosity of a 1g./100ml. solution in chloroform = 0.11), there was no dead period, and tetragastrin was released continuously from time zero ( $T_0$ ).

15 A.1.2. Similar formulations were manufactured using 10% by weight of the synthetic luliberin analogue ICI.118,630,  $\square$  Gln-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-NH<sub>2</sub>, molecular weight = 1269, in place of tetragastrin.

20 With a prior art polylactide of  $M_w \sim 240,000$  (intrinsic viscosity = 1.36), the release of the polypeptide was biphasic, with a dead period of about 15 days.

25 With a novel polylactide of  $M_w \sim 15,000$  (intrinsic viscosity = 0.25), there was a short induction period, followed by continuous release.

30 With a novel polylactide of low  $M_w$  (inherent viscosity of a 1g./100ml. solution in chloroform = 0.11), there was continuous release from  $T_0$ .

A.2. Medium molecular weight polypeptide. Formulations were manufactured comprising 0.1% by weight of mouse epidermal growth factor (EGF), molecular weight = 6041, in

81/08

- 14 -

polylactides comprising equimolar proportions of D,L-lactic acid and glycolic acid units, and of different  $M_w$ , and placed in pH 7.4 buffer. Release of EGF was monitored by radio-immunoassay.

With a prior art polylactide of  $M_w \sim 200,000$  (intrinsic viscosity = 1.08), there was no initial release, and no significant release of polypeptide until between 13 and 20 days after  $T_0$ , after which release was continuous.

With a novel polylactide of  $M_w \sim 80,000$  (intrinsic viscosity = 0.58), there was also no initial release, and significant release did not occur until between 6 and 10 days after  $T_0$ , after which release was continuous.

With a novel polylactide of low  $M_w$  (inherent viscosity of a 1g./100ml. solution in chloroform = 0.11), there was continuous release from  $T_0$ .

A.3. High molecular weight polypeptide.

A formulation was manufactured comprising 20% w/w of bovine prolactin, molecular weight  $\sim 22,000$ , in a novel polylactide comprising equimolar proportions of D,L-lactic acid and glycolic acid units, and of low  $M_w$  (inherent viscosity of a 1g./100ml. solution in chloroform = 0.11).

As expected from previous experiments A.1.1, A.1.2 and A.2, this formulation also released polypeptide continuously from  $T_0$  when tested in vivo in rats, and circulating bovine prolactin assayed by radio-immuno assay.

- 15 -

Experiments A:1 to A.3 thus demonstrate that reducing the molecular weight,  $M_w$ , or viscosity of the polylactide used in the manufacture of a composition reduces the biphasicity of polypeptide release, for polypeptides of low or medium molecular weight, or the initial delay in release of polypeptides of medium or high molecular weight, and achieves a continuous release of the polypeptide from  $T_0$ .

10 B. Ratio of lactide/glycolide in the polylactide.

Compositions were manufactured in the form of implants containing 100 $\mu$ g. (3% w/w) of the luliberin analogue ICI. 118,630 in polylactides of  $M_w \sim 300,000$  but of different lactide/glycolide ratios. All of these formulations when tested in vivo in adult female rats exhibiting normal oestrous behaviour, gave biphasic release of the polypeptide, comprising release for about 6 days post-treatment, followed by a dead period, during which there was no significant polypeptide release. The length of this dead period decreased with decreasing lactide/glycolide ratio (L/G), as follows:-

L/G	Dead period(days)
100/0	no release
75/25	51
67/33	34
50/50	15



- 16 -

This experiment thus indicates that a composition exhibiting a biphasic release of polypeptide can be improved in the direction of achieving continuous release by increasing the proportion of glycolide to lactide in the polylactide used, up to about 50% glycolide.

C. Ratio of polypeptide to polylactide.

Compositions in the form of implants were manufactured using different concentrations of the synthetic luliberin analogue, ICI.118,630, in a prior art 50/50 lactide/glycolide polylactide of  $M_w \sim 200,000$ , and tested in vivo in rats as described above. At 5% and 10% w/w incorporation, the release of polypeptide was biphasic, but at 15% and 20% incorporation, the biphasicity disappeared.

This experiment thus demonstrates that a polylactide of high molecular weight, which gives biphasic release of polypeptide when the polypeptide is incorporated only at low levels, can be used to make satisfactory continuous release formulations if the proportion of polypeptide is increased sufficiently.

D. Molecular weight distribution.

A solution of a polymer blend of wide molecular weight distribution (polydispersity) was obtained by mixing solutions of a 50/50 D,L-lactide/glycolide polylactide of low  $M_w$ , (reduced specific viscosity of a 1g./100ml. solution in chloroform = 0.115), (3 parts by weight) and a 50/50 D,L-lactide/glycolide polylactide of  $M_w = 200,000$ , (intrinsic viscosity = 1.08), (1 part by weight). Tetragastrin

- 17 -

(1 part by weight) was added, and the mixture was cast to give a polylactide/tetragastrin composition containing 20% by weight of tetragastrin, and this was then moulded to give a slab 0.02cm. thick. The slab was placed in water at 37°C. and the release of tetragastrin was found to be continuous from  $T_0$ , and to continue for at least 44 days.

Poly lactides of wide molecular weight distribution may be obtained either by mixing preformed polymers of different molecular weights, or by appropriate control of the polymerisation process in generally known manner, and such poly lactides confer important advantages, for example the lower molecular weight polylactide species allow an essentially immediate release of some polypeptide, while the higher molecular weight polylactide species both extend the release period and slow down the overall rate of release of the polypeptide. In addition, the blending of low and high  $M_w$  fractions modifies the water absorption characteristics of the polylactide in a parallel manner.

E. Thickness of the implant.

E.1. A solution of 10% by weight of tetragastrin in a polylactide comprising equimolar proportions of D,L-lactic acid and glycolic acid units, and of  $M_w \sim 15000$  was cast into films 0.02, 0.06 and 0.12 cm. thick. All three films showed continuous release of tetragastrin from  $T_0$ , and at 28 days, the three films had released respectively 85, 75 and 66% of their tetragastrin content.

- 18 -

E.2. The uptake of tritiated water from pH 7.4 buffer by slabs of polylactide comprising equimolar proportions of D,L-lactic acid and glycolic acid units of  $M_w \sim 200,000$ , and intrinsic viscosity = 1.08 and of thickness 0.02, 0.06, 0.12 and 0.20 was measured by removing such slabs from the buffer solution successively after varying times of immersion, and measuring the tritium content by scintillation counting. After 5 weeks, the different thickness slabs had absorbed respectively 44, 20, 15 and 11% by weight of water.

These experiments show how the thickness of the implant can be used to control the absorption of water by, and thus the rate of release of polypeptide from, a composition of the invention, thicker implants releasing the polypeptide more slowly than thinner ones.

As indicated above the composition of the invention may be formulated as a solid composition for sub-dermal injection or implantation or as a liquid formulation for intramuscular or subcutaneous injection.

Suitable solid compositions for sub-dermal injection or implantation are, for example, rods, spheres, films or pellets, and cylindrical rods which can be injected through a hypodermic needle or trochar are preferred. Such compositions are manufactured by conventional techniques which are well known in the pharmaceutical art.

- 19 -

Preferred solid compositions of the invention, for polypeptides within different molecular weight ranges, are as shown in Table 1, and preferred compositions for specific polypeptides of particular interest are as shown in Table 2. Each entry in Tables 1 and 2 thus defines a further feature of this invention.

TABLE 1

No.	Polypeptide M.W.	Polylactide Inherent Viscosity	Glycolide Lactide	% Poly- peptide	Preferred % Poly- peptide
1.	<2000	>0.5	0.5-3	5-50	
2.	<2000	0.2-0.5	0.2-3	5-50	10-30
3.	<2000	<0.2	0-3	0.1-50	
4.	1500-10,000	0.4-0.8	0.5-3	10-50	20-50
5.	1500-10,000	0.15-0.4	0.2-3	5-30	10-30
6.	1500-10,000	<0.15	0-3	0.1-20	1-20
7.	8000-30,000	0.15-0.4	0-3	0.1-50	
8.	8000-30,000	0.1-0.15	0.7-3	10-50	
9.	8000-30,000	<0.1	0-3	0.1-50	

TABLE 2

No.	Polypeptide	Poly lactide Inherent Viscosity	Glycolide Lactide	% Poly- peptide
10.	Tetragastrin	>0.5	1-3	5-50
11.	Tetragastrin	0.2-0.5	0.5-3	5-50
12.	Tetragastrin	<0.2	0-3	0.1-50
13.	ICI.118630	>0.5	0.8-3	5-50
14.	ICI.118630	0.2-0.5	0.2-3	5-50
15.	ICI.118630	<0.2	0-3	0.1-50
16.	EGF	0.4-0.8	0.5-3	10-50
17.	EGF	0.15-0.4	0-3	0.1-50
18.	Prolactin	<0.15	0-3	0.1-50

Also as indicated above, the composition of the invention ~~may also be formulated~~ as a suspension for injection. Such suspensions may be manufactured by general techniques well known in the pharmaceutical art, for example by milling the polylactide/polypeptide mixture in an ultracentrifuge mill fitted with a suitable mesh screen, for example a 120 mesh, and suspending the milled, screened particles in a solvent for injection, for example propylene glycol, water optionally with a conventional viscosity increasing or suspending agent, oils or other known, suitable liquid vehicles for injection.

- 21 -

The continuous release of ICI.118630 from a suspension composition of the invention was demonstrated by comparing the dioestrous behaviour of normal mature female rats dosed subcutaneously with either a

5 propylene glycol suspension of particles milled to 120-mesh size and containing 3% by weight of ICI.118630 in a polylactide comprising equimolar proportions of D,L-lactic acid and glycolic acid units, and a  $M_w \sim$  240,000, (intrinsic viscosity = 1.36), or with a saline

10 solution of 100, 200 or 300 $\mu$ g. of ICI.118630 per animal. With the saline solutions, there was an immediate short period of dioestrus, but after 3 days post-dosing normal cyclicity was re-established. With the suspension composition of the invention, by contrast, the animals

15 were substantially in dioestrus for about 40 days. Similar results were obtained with an injection formulation based on a mixture of 1% of ICI.118630 in a similar polylactide having an intrinsic viscosity of > 0.5.

20 Thus, according to a further feature of the invention there is provided a suspension formulation comprising from 1 to 50% by weight of a solid formulation, which itself comprises from 0.1 to 50% by weight of an acid-stable polypeptide as herein defined and from 50 to

25 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0 to 3 and which is either soluble in benzene and has an inherent viscosity (lg./ 100ml. solution in benzene) of less than 0.5 or is insoluble in benzene and has an inherent viscosity (lg./

30 100ml. solution in chloroform or dioxan) of less than 4, which solid formulation has been reduced to fine particle size, together with from 50 to 99% by weight of a liquid carrier suitable for injection into mammals.

- 22 -

It is to be noted that, because of the reduced particle size of the polypeptide/polylactide in a suspension for injection, certain solid formulations, which are not suitable for implantation, are rendered  
5 useful when reduced to fine particle size and formulated as a suspension for injection. For example, the two particular suspension formulations referred to above both contain less ICI.118,630 than has been found acceptable for implantable formulations, as shown in  
10 Tables 1 and 2 above.

From the foregoing, it is clear that it is desirable to manufacture polylactides of a range of  $M_w$ , particularly of low to medium  $M_w$  in the range up to 60,000, and of high polydispersity  $\left(\frac{M_w}{M_n}\right)$ , these  
15 being particularly valuable in the compositions of this invention. The prior art relating to polylactides in general, and to copolymers containing lactic acid and glycolic acid units in particular, is silent as to the manufacture of such copolymers of low molecular weight,  
20 and as to methods of achieving high polydispersity in such copolymers. Indeed, it is inherent in the prior art disclosure of polylactides that they are generally of  $M_w$  greater than about 30,000-60,000 (an inherent viscosity of greater than 0.5) and of low polydispersity, due to  
25 their manufacture under anhydrous conditions and without any added chain-stoppers. We have realised that, because of the different reactivities under polymerisation conditions of the cyclic dimers of lactic acid and glycolic acid, copolymers of high  
30 heterogeneity in respect of polymer species may be obtained by ring opening polymerisation of a mixture of the two cyclic dimers in the presence of chain-

- 47 -

14. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 0.1 to 50% by weight of a polypeptide of molecular weight 8,000 to 30,000 and from 50 to 99.9% by weight of a polylactide wherein the  
5 ratio of glycolide to lactide units is 0 to 3, and which has an inherent viscosity of less than 0.1.

15. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 5 to 50% by weight of ICI.118,630 and from 50 to 95% by weight of a polylactide  
10 wherein the ratio of glycolide to lactide units is 0.8 to 3, and which has an inherent viscosity of more than 0.5.

16. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 5 to 50% by weight of  
15 ICI.118,630 and from 50 to 95% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0.2 to 3, and which has an inherent viscosity of 0.2 to 0.5.

17. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 0.1 to 50% by weight of  
20 ICI.118,630 and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0 to 3, and which has an inherent viscosity of less than 0.2.

25 18. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 10 to 50% by weight of epidermal growth factor or urogastrone and from 50 to 90% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0.5 to 3, and which has an  
30 inherent viscosity of 0.4 to 0.8.



19. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 0.1 to 50% by weight of epidermal growth factor or urogastrone and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0.3, and which has an inherent viscosity of 0.15 to 0.4.

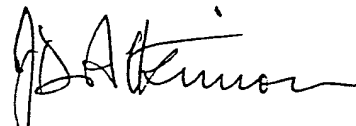
20. A pharmaceutical composition in the form of a suspension for injection comprising from 1 to 50 % by weight of a solid formulation, which itself comprises from 0.1 to 50% by weight of an acid-stable polypeptide as herein defined and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0 to 3 and which is either soluble in benzene and has an inherent viscosity (lg./100ml. solution in benzene) of less than 0.5 or is insoluble in benzene and has an inherent viscosity (lg./100ml. solution in chloroform or dioxan) of less than 4, which solid formulation has been reduced to fine particle size, together with from 50 to 99 % by weight of a liquid carrier suitable for injection into mammals.

21. A heterogeneous copolymer of lactic acid and glycolic acid units comprising from 25 to 100% molar of lactic acid units and from 0 to 75% molar of glycolic acid units, and which is either soluble in benzene and has an inherent viscosity (lg./100ml. solution in benzene) of less than 0.5, or is insoluble in benzene and has an inherent viscosity (lg./100ml. solution in chloroform or dioxan) of less than 4.

22. A process for the manufacture of a heterogeneous copolymer as claimed in claim 21 which comprises the ring opening copolymerisation of a mixture of the cyclic dimers of lactic acid and glycolic acid.

- 49 -

23. A heterogeneous copolymer as claimed in claim 21 whenever prepared by the process claimed in claim 22.



JOHN DAVID ATKINSON

AUTHORISED REPRESENTATIVE  
General Authorisation No. 97



European Patent  
Office

# EUROPEAN SEARCH REPORT

0058481

Application number

EP 82 30 0416.3

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D	US - A - 3 773 919 (BOSWELL et al.)		A 61 K 37/02
X	* examples 3, 6; column 8, lines 6 to 12 *	21-23	C 08 G 63/08
Y	* abstract; column 2, line 60, column 8, line 6 to column 11, line 49 *	1-20	/C 07 C 103/52
Y	Chemical Abstracts vol. 88, no. 12, March 1978 Columbus, Ohio, USA T.M.S. CHANG "Biodegradable semipermeable microcapsules containing enzymes, hormones, vaccines, and other biologicals" page 79044, column 2, abstract no 79041n & J. Bioeng. vol. 1, no. 1, 1976, pages 25 to 32	1-20	A 61 K 31/765 A 61 K 9/22
D,A	US - A - 3 887 699 (YOLLES) * claim 1; column 5, line 4; column 6, line 15 *	1-23	
A	US - A - 4 011 312 (REUTER et al.) * examples *	21-23	
P,A	EP - A2 - 0 025 698 (ELI LILLY AND CO.) * examples 1 to 7 *	21-23	
			TECHNICAL FIELDS SEARCHED (Int.Cl. 3)
			A 61 K 9/22 A 61 K 31/765 A 61 K 37/02 C 08 G 63/08
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			&: member of the same patent family, corresponding document
Place of search Berlin		Date of completion of the search 10-05-1982	Examiner BREW



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	Chemical Abstracts vol 91, no. 2, 1979 Columbus, Ohio, USA D. WISE et al. "Results on biodegradable cylindrical subdermal implants for fertility control" page 275, column 2, abstract no. 9442g & MIDL. Macromol. Monogr., vol. 5 (Polym. Delivery Syst.), 1978, pages 121 to 138	21-23	
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
A	GB - A - 2 008 135 (ETHICON, INC.) * complete document *	21-23	